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Difficulties in the Electrocardiographic Diagnosis of Myocardial Infarction: The earliest electrocardiographic classifications of myocardial infarction included only anterior and posterior localizations. Since then, the ECG picture of myocardial infarction involving the anteroseptal, anterolateral, posterolateral, postero-inferior, high lateral, and septal involvement extending from the anterior to the posterior aspects of the heart have been clearly defined and correlated with postmortem findings. The ECG patterns resulting from auricular infarction, and from the presence of infarction limited to the right ventricle, also have been described.

The purpose of the present article is to describe those conditions in which the ECG diagnosis of myocardial infarction might be rendered difficult. Most of the material for this report was secured by making comparisons between the ECG interpretations and the pathologic change in the hearts of patients who were found to have myocardial infarcts at necropsies performed at the Charity Hospital of Louisiana in New Orleans during the 2 years prior to this report. There were 519 patients admitted during this period for whom the diagnosis at the time of discharge or death was myocardial infarction. One hundred sixty-four of these patients died, and postmortem examination was performed on 61. There were 13 instances of marked discrepancy between the ECG interpretation and the autopsy findings.

Routine ECGs consist of at least the 3 standard leads and the precordial leads V_1 through V6. In certain patients the potential was determined at the ensiform cartilage, at the anterior and lateral aspects of the left third and fourth intercostal spaces, across the posterior chest wall, at various other points on the chest wall, and in the esophagus. The ECGs were re-examined whenever the postmortem findings did not confirm the ECG interpretation, in order to see if any satisfactory explanation for the discrepancy could be found.

Septum. The ECG on J. B. shows a complete heart block with idioventricular rhythm. At postmortem examination infarction limited to the septum was found. There are certain regions of the myocardium in which absence of activation because of dead muscle may not cause readily recognizable changes in the limb leads or 6 standard precordial leads. One of these areas is the septum. A lesion, if limited to the septum, will not necessarily produce ECG changes which can be interpreted as evidence of myocardial infarction. Although bundle branch block, complete heart block, or prolongation of the P-R interval may result, these findings alone cannot be considered as ECG confirmation of a diagnosis of coronary occlusion.

From theoretical considerations one might expect to observe disappearance of the normal small Q1 in counterclockwise rotated hearts (or of Q3 in clockwise rotated hearts) in which the septum is infarcted with resulting absence of the initial electromotive forces incident to activation of the septum. These initial forces are normally so oriented that positivity is directed toward the right side

of the septum, this being attributable to either earlier activation or a larger area of simultaneous activation on the left side of the septum. The absence of the initial R wave in leads from the right ventricle obtained by cardiac catheterization might suggest septal infarction. Septal infarctions which extend to the anterior or to the posterior walls usually produced characteristic ECG patterns. Recently, the ECG picture of septal infarction extending to both the anterior and posterior aspects of the heart has been described. ECG changes indicating simultaneous involvement of the anterior and posterior walls adjacent to the septum suggest this diagnosis.

High Posterior. The ECG on A. S. shows only RS-T segment elevation in leads I and V_6, and depression of the segment in V_2, V_3, and V_4; postmortem examination, however, revealed a hemopericardium as a result of leakage from a 5-cm. area of infarction on the posterior aspect of the left ventricle, extending inferiorly from the A-V junction. Infarction involving the superior portion of the posterior wall of the left ventricle adjacent to the A-V junction may not cause changes in the ECG because absence of normal electrical activity in this region may not result in QRS changes characteristic of infarction. This is especially true in clockwise rotated, apex-back, vertical hearts, in which the resultant electrical components derived from this area are normally directed largely peripendicularly to the frontal plane. Esophageal ECGs might be helpful in this type of patient.

High Lateral. The ECG taken on J. R. shows characteristic QRS changes in leads taken above the usual V_1 through V_6 positions. Myocardial infarction involving the superior portion of the lateral wall of the left ventricle may be missed unless precordial leads are taken in areas above the usual V_4 through V_6 positions. This area of infarction has been designated high lateral infarction.

Right Ventricle. The ECGs on L. F. show a QS wave in V_1, V_2, and V_3, and possible incomplete left bundle branch block. On postmortem examination massive infarction of the right ventricle with septal involvement was found. Infarctions involving the right ventricle may be suggested by changes in V_1 and leads taken superior to the V_2 and V_3 positions.

Auricular. Changes in the P wave and P-R segment have been described in auricular infarction. In none of the authors' patients with auricular involvement were these changes demonstrated, although an ectopic pacemaker appeared in E. W. who had an area of infarction involving the right auricle.

Small Anterior Infarction. The ECG on A. W. shows relatively low R waves in V_2 and V_3. At necropsy there was found a 3- by 4-cm. myocardial infarction anteriorly just to the left of the interventricular groove. The ECG on E. W. shows relatively low R waves in V_2 and V_3. At autopsy there was a 3-cm. area of infarction with softening of the anterior surface of the left ventricle. In certain patients with small areas of anterior myocardial infarction the ECG may not be characteristic of infarction. The failure of the R wave to increase in amplitude in the usual fashion as the electrode is moved from the right to

the left precordium, or the presence of a QS wave in V_1 and V_2, may be attributed to left ventricular hypertrophy or to an apex-back position of the heart. The presence of an initial R wave in Lead V_{3R} and V_E when a QS complex is present in V_1 and V_2 may help to indicate the presence of an anterior infarct.

Multiple Infarctions. The ECG on O. J. shows right bundle branch block and T-wave changes suggestive of myocardial ischemia. Necropsy revealed numerous myocardial infarctions, averaging about 1.0 by 0.2 cm. in size, in all sections of the left ventricle and interventricular septum. Scattered small infarcts in the left ventricle should not produce characteristic changes suggesting myocardial infarction because the absence of electrical effects in these areas will not cause sufficient alteration in the pathway of the wave of accession to result in an ECG pattern suggesting myocardial infarction. The postmortem examination of A. V. B. revealed an area of old infarction involving the posterior wall of the left ventricle. There was also an area of recent infarction involving the apical region. The ECG evidence of posterior infarction was obscured. There are patients who have multiple areas of infarction in which the effects of one area predominate and make the diagnosis of another area of infarction impossible. In rare instances there are 2 areas of myocardial infarction of similar size involving diametrically opposed areas of the left ventricle, so that the electrical changes in one wall are to some extent counterbalanced by change in the opposite wall. Serial studies of patients with multiple episodes of myocardial infarction will usually enable one to localize the lesion accurately, despite the fact that the final ECG may show QRS changes of the predominant area of infarction only.

Intramural Infarctions. The ECG on V. M. shows no abnormalities to suggest myocardial infarction. At autopsy a large intramural infarction was found involving most of the posterior wall of the left ventricle. The QRS magnitude found in leads taken over the posterior chest wall in this patient was well below the average range of QRS magnitudes found in a large series of normal patients. A region of infarction which is completely intramural will usually not cause characteristic changes associated with myocardial infarction. The wave of accession will be altered, but the initial forces of activation in the subendocardial areas may cause an upright deflection in the leads which face the area of infarction, so that the prominent Q wave, suggesting dead muscle tissue, is absent. The effects of injury in a completely intramural infarction may also not produce characteristic RS-T segment displacements. Postmortem examination on M. W. showed an area of infarction on the lateral aspect of the heart involving the outer third of the myocardium. The ECG shows a prominent, wide S wave in leads V_4 and V_5. Postmortem examination on J. H. showed a 4.5-cm. area of old infarction on the posterolateral aspect of the left ventricle extending from the epicardium inward and involving the outer one half of the myocardium. The ECG shows a prominent S wave in leads II, III, V_4, V_5, and V_6. Because the initial spread of excitation from the endocardium outward is not affected in this type of lesion, a Q wave will not appear and only a reduction in the amplitude of the R wave or the appearance of an S wave in the leads which face the infarcted area may occur.

Bundle Branch Block. In the presence of bundle branch block the characteristic QRS changes produced by myocardial infarction are modified. Bundle branch block may in itself be caused by the presence of septal infarction. In left bundle branch block the ECG changes indicating myocardial infarction are rarely diagnostic. If left bundle branch block is present, initial activation of the septum occurs on its right side, and the left arm and left lateral precordium face the positive side of the wave of accession. This results in an absence of a Q wave in Lead I and in the left lateral precordial leads in most cases. The appearance of a Q wave in these leads in left bundle branch block suggests the possibility of septal infarction; however, this may also occur as a result of clockwise rotation of the heart on its longitudinal axis as viewed from the apex. Although, in the presence of left bundle branch block, a diagnosis of septal infarction has been suggested in 2 of the authors' patients on the basis of prominent Q wave in Lead I and in the left precordial leads, autopsy was not obtained on either of them. In some of the authors' cases in which patients whose ECGs show left bundle branch block the appearance of segment shifts as a result of the effects of injury, and variation in the QRS configuration in serial ECGs over a period of weeks, suggest the presence of myocardial infarction. Because postmortem examination was not made in any of these cases, the authors were not able to confirm their interpretation. Right bundle branch block usually does not obscure the changes produced by infarction of the left ventricle.

Ventricular Tachycardia. There were 2 patients with myocardial infarction in the series in whom initial ECGs show ventricular tachycardia. Postmortem examination on G. P. showed an area of recent infarction involving the apex of the septum and the surrounding circumapical area of ventricular muscle. There was no history to suggest infarction for W. M., but postmortem examination showed an area of recent massive infarction involving the posterior, lateral, and circumapical areas of the left ventricle. Paroxysmal ventricular tachycardia may render the ECG diagnosis of myocardial infarction difficult. Although the appearance of ventricular tachycardia itself may suggest a diagnosis of myocardial infarction, the presence of this arrhythmia may preclude ECG confirmation of the diagnosis.

Other Conditions. In complete heart block with an idioventricular rhythm, or in any mechanism disturbance in which initial activation occurs in the ventricles, the QRS changes caused by infarction may be masked.

Impending Infarction. The authors have observed one patient, E. W., whose ECG shows characteristic QRS changes and RS-T segment shifts, indicating anterolateral myocardial infarction, in whom necropsy, including detailed microscopic sections, did not reveal any areas of myocardial infarction although there was stenosis of both coronary ostia. In rare instances the ECG picture usually associated with recent myocardial infarction may be seen when no area of myocardial infarction can be found at postmortem examination. Although the ECG may show the pattern of recent myocardial infarction, actual death of the muscle may not have occurred before exitus. Hence, at postmortem

examination, tissue destruction may not be evident, although minor alterations in the muscle fibers may be detectable. In these cases the fibers in the involved region are severely injured, but not dead. The Q waves of the type seen in infarction then may be ascribed to slow invasion of the affected area by the wave of excitation together with a state of partial depolarization of the injured muscle. Blocking of the wave of excitation within the area may or may not occur.

Changes in Muscle Not a Result of Coronary Atherosclerosis. Conditions other than atherosclerotic disease of the coronary arteries should be mentioned in a discussion of myocardial infarction. ECGs made during attacks of angina pectoris may closely simulate those recorded in the early stages of myocardial infarction. An ECG picture of myocardial infarction may result from occlusion of the coronary arteries from various types of embolism (such as air, fat, and those composed of caseous matter), or from disease of the wall of the coronary arteries (such as that caused by extrinsic pressure, Buerger's disease, periarteritis nodosa, anaphylactic conditions, or rheumatic arteritis, syphilitic arteritis, or any other infectious process). Metastatic carcinoma, primary neoplasms of the heart, tuberculoma, gumma, trauma, and other conditions which cause a localized destruction of heart muscle might produce an ECG picture similar to that of infarction.

Pulmonary Embolism. The serial tracings on B. H. show the appearance of a prominent Q3. At postmortem examination multiple pulmonary emboli were found but no evidence of myocardial infarction. ECGs taken on patients with pulmonary embolism occasionally resemble the pattern of posterior infarction. Inversion of the T waves in leads over the right ventricle and serial tracings will often help in the differentiation of these 2 conditions. Occasionally infarction in other areas of the myocardium may be simulated by pulmonary infarction. The serial ECGs on G. K. reveal a sudden development of a prominent S wave in lead I together with a marked right axis deviation and prominent S waves over the precordium. Subsequent pictures show a return of the QRS configuration to its previous form. G. K. had a pulmonary embolism following a gastric resection. The appearance of a marked right axis deviation with prominent S waves over the precordium can be explained on the basis of right ventricular dilatation with rotation of the heart clockwise as viewed from the apex, so that the right ventricle faces the anterior and lateral portions of the left side of the chest, and the left ventricle is displaced to the right and posteriorly. Serial ECGs on F. I. show similarly marked QRS changes following pulmonary embolism. The appearance of a large S wave in leads I, V_5, and V_6, and a relatively high R wave in leads III and V_1 resulted from right ventricular dilatation with clockwise rotation.

Heart Position. The ECG picture of a healed posterior myocardial infarct is occasionally difficult to differentiate from a normal tracing in a patient whose heart is in a horizontal, slightly clockwise, rotated position.

In conclusion, changes in the QRS complexes indicating infarction are of primary importance in obtaining ECG confirmation of this condition. T-wave

and RS-T segment changes alone are not sufficient to indicate the presence of dead cardiac muscle. T-wave inversion alone may merely reflect a stage of ischemia, and RS-T segment changes alone may signify a state of injury; however, unless QRS changes appear, and persist, one is rarely justified in making an ECG interpretation of myocardial infarction.

Routine ECGs should include the 3 standard leads and at least precordial leads V1 through V6. In patients whose clinical history suggests infarction, if these leads are not confirmatory, additional exploration with other precordial leads should be undertaken. Serial ECGs furnish valuable information. Whereas changes in a single ECG may not be confirmatory of a diagnosis of infarction, serial pictures demonstrating a progression of changes may be diagnostic.

The cases presented in this paper demonstrate that an ECG is still only a laboratory procedure which is an adjunct to the confirmation of a clinical diagnosis of myocardial infarction and should not be relied on completely to establish or disprove a diagnosis of coronary occlusion. Although serial ECG changes of infarction are highly characteristic, their absence does not rule out a diagnosis of myocardial infarction. Too frequently the authors have seen a diagnosis of myocardial infarction resting on T-wave changes alone, and conversely the absence of ECG changes used as the only negative evidence in ruling out a diagnosis of coronary occlusion in a patient whose history and other laboratory findings were practically diagnostic of myocardial infarction. Although most patients with myocardial infarction will have ECGs which will confirm this diagnosis, it is well to remember that occasionally the ECG will show no characteristic changes in patients with myocardial infarction. (Am. Heart J., Feb. '50, L. Levy and A. L. Hyman)

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The Clinical Importance of Coagulase-Positive, Penicillin-Resistant Staphylococcus Aureus: Penicillin-resistant Staphylococcus aureus has been isolated with increasing frequency since the introduction of this agent in 1941.

Barber and Rozwadowska-Dowzenko, in a recent study of S. aureus infections, observed a progressive increase in the yield of penicillin-resistant strains from 14 percent in 1946 to 59 percent in 1948. Hirsh et al. reported 4 cases of bacteremia or endocarditis resulting from penicillin-resistant, coagulase-positive S. aureus. In each case resistance developed after penicillin therapy was begun. Nichols and Needham, early in 1949, reported 34 of 50 recently siolated strains, or 68 percent, to be penicillin-resistant.

In this study, 56 percent of 64 strains of coagulase-positive S. aureus obtained from clinical material between August 1948 and May 1949 were penicillin-resistant. The data accumulated confirm the observations of Barber and Rozwadowska-Dowzenko, and Nichols and Needham, and further emphasize the fact that there has been a steady increase in the relative number of infections caused by penicillin-resistant strains of S. aureus.

Some difference in opinion has arisen regarding the origin and transmission of penicillin-resistant S. aureus. North and Christie demonstrated that penicillin-sensitive and penicillin-resistant strains successively recovered from the same person were of the same bacteriophage type. They concluded that the resistant organisms were composed of descendants of the sensitive parent strain. Barber and Rozwadowska-Dowzenko noted a similar chain of events but also, on 2 occasions, isolated resistant S. aureus, the type of which differed from that of the original sensitive organism. Miller has suggested that resistant bacteria readily act as secondary invaders of infections in patients treated with penicillin. The observation of Harley and his associates that hospital infection of wounds provided the highest incidence of penicillin-resistant S. aureus supports this view. Hospital cross-infection was apparently responsible for over half the cases of Barber and Rozwadowska-Dowzenko yielding penicillin-resistant S. aureus in which the drug had not previously been given.

In this study, there was a close correlation between the isolation of resistant strains and previous administration of penicillin, but 20 percent were recovered from persons in whom this drug had not been given. Of the nasal carriers reported, 29.4 percent yielded penicillin-resistant S. aureus. None of these healthy subjects had received penicillin, but most were in recent contact with hospital environments. Martyn recovered penicillin-resistant, coagulase-positive S. aureus by nasopharyngeal culture from 56.5 percent of 81 healthy newborn infants. None had received penicillin, but all were in a hospital.

The question must immediately be raised whether the present high incidence of infection by penicillin-resistant S. aureus is of serious clinical import. Strains of this organism that have been made insensitive to the action of the drug in vitro are of low invasiveness and have characteristics different from those of the parent organism. This is not so when the organisms have been isolated in cases of human disease. Investigation of experimental infection in mice has demonstrated that such staphylococci are capable of producing fatal illnesses that are not favorably altered by the administration of penicillin.

Few reports have appeared describing therapeutic failures as the result of infection by penicillin-resistant S. aureus. Twelve of 15 successive examples of staphylococcal sepsis with bacteremia, recently studied by Nichols and Needham at the Mayo Clinic, were caused by highly penicillin-resistant staphylococci. The course of these illnesses was not affected by the usual amounts of penicillin. Similarly, this agent was ineffective in the 2 cases of staphylococcal sepsis described in this report. Furthermore, it is of importance to note that the organism was isolated from the blood on 7 occasions during the period of this investigation; 6 of the isolated strains were resistant to penicillin. The remaining examples of serious staphylococcal disease described in this paper do not permit an evaluation of the effect of the penicillin resistance of the etiologic agent on the efficacy of therapy with this antimicrobial agent. Barber and Rozwadowska-Dowzenko have described 2 cases of fatal

sepsis caused by S. aureus with bacteremia, in both of which intensive penicillin therapy was ineffective. In one case renal insufficiency led to the development of penicillin blood levels of 8 units per cubic centimeter. A similar unfavorable result was obtained by McLetchie in 2 cases of pneumonia caused by penicillin-resistant S. aureus in infants.

Information presently available does not indicate that the staphylococci carried by the population at large are frequently resistant to penicillin. It is clear, however, that persons who have received this drug, or who have been hospitalized or in contact with hospital environments, are likely to harbor resistant staphylococci or to suffer infections caused by them. It is of the greatest importance that penicillin-sensitivity tests be carried out during the study of infections that develop in patients in any of these categories. If this is not done, valuable time may be lost in treatment with penicillin, which will then be proved to be useless.

Investigation for the purpose of determining the efficacy of other antimicrobial agents in the treatment of patients with staphylococcal disease caused by penicillin-resistant organisms is obviously of the greatest importance. Nearly all such strains that have been studied have been inhibited by low concentrations of streptomycin. The 2 cases described demonstrate that this agent may not be particularly effective in the management of serious staphylococcal sepsis. Rapidly developing bacterial resistance to the drug will doubtless be the cause of failure in most cases. Studies in the authors' laboratory and by Lankford and Lacy, as well as by Nichols and Needham, indicate that penicillin-resistant staphylococci will be readily inhibited by aureomycin in vitro. The latter investigators have reported the successful treatment with aureomycin of 4 out of 6 patients with generalized staphylococcal infections. A similar case is described in this report. Not yet evaluated is the possible role of combined antibiotic therapy in such cases. Concurrent administration of aureomycin and streptomycin may well be of value, for the latter agent might be expected to inhibit the growth of highly streptomycin-resistant mutants as they appear, in addition to having striking antibacterial action in itself. (New England J. Med., 9 March '50, P. M. Beigelman and L. A. Rantz)

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Re-evaluation of Ethyl Alcohol as a Germicide: Ethyl alcohol remains the most popular of skin disinfectants because by and large it is the best. Inexpensive, readily obtainable, harmless to the skin and bacteriologically potent, its chief deficiency lies in its inability to kill spores, a deficiency shared by all the commonly used skin disinfectants. That its bactericidal power varies with the concentration of the solution used is well known, but what constitutes the most effective alcohol-water ratio has long been a moot question.

According to Epstein, 50 percent by volume is best. Harrington found, however, that from 60 to 70 percent by volume is the optimum concentration

against dry test bacteria and that stronger concentrations are equally efficacious when the bacteria are wet. Beyer, who was first to point out the advantages of preparing alcohol solutions by weight rather than by volume, observed that 70 percent by weight was by far the most powerful concentration against dry staphylococci. His conclusions were corroborated by Gregersen, but Christiansen concluded that 80 percent by weight was better. Still other opinions were voiced by other investigators.

A new effort has been made to settle finally the old but still controversial question of the germicidal value of ethyl alcohol. This is a matter of practical importance because alcohol is universally employed as a skin disinfectant and as a solvent for other germicidal agents and not infrequently also as the solution of choice for cold sterilization of "sharps" and other instruments.

In vitro studies, using the quantitative "spoon test" with bacteria in aqueous suspension, have shown that some concentrations of alcohol are impotent but that others are strongly and rapidly germicidal. In general, 10 and 20 percent solutions by weight have little or no bactericidal effect in 10 minutes or less at room temperature; 30, 40, and 50 percent solutions show progressively greater germicidal power, and from 60 to 90 percent solutions by weight are all strongly and rapidly bactericidal, much of the killing effect apparently taking place during the first few seconds of contact. Absolute alcohol is somewhat less effective. Staphylococcus albus, obtained from the resident flora of the skin, was observed to be more resistant to ethyl alcohol than either Staphylococcus aureus or Escherichia coli taken from stock laboratory cultures. Spores of various sorts were found to be highly resistant to all concentrations of alcohol at room temperature, although vegetative forms of the same organisms were killed.

Various concentrations of alcohol have also been tested thoroughly under conditions of actual use on the hands and arms of several persons. Solutions of 60 percent by weight and stronger were all shown to be efficient skin disinfectants. The optimum concentration varied with different persons, and even in the same person from time to time, probably because of variations in the flora and condition of the skin.

Seventy percent alcohol by weight is still believed to be the solution of choice for disinfection of the skin. In addition to being powerfully germicidal, this solution spreads well, dries slowly, does not extract cutaneous fats, is almost perfectly innocuous on healthy skin, and is proportionately less expensive than higher concentrations. It is recommended that the operator, in preparing for surgical procedures, after a thorough scrub, dry his hands and arms with a sterile towel and then wash in 2 solutions of alcohol with washcloth friction, first briefly in a basin of 95 percent by volume (commercial) alcohol and then for 2 or 3 minutes in a basin of 70 percent alcohol by weight. If the skin is healthy, that simple routine will scarcely fail to reduce its bacterial count greatly (to approximately 1 or 2 percent of the original number), whatever the initial size or specific composition of the flora.

Ethyl alcohol should not be used as a disinfectant in wounds or on raw surfaces, for it is painful, it injures the tissues, and its antibacterial action is neutralized by proteins present in the wound.

Because simple solutions of ethyl alcohol tend to rust metal and cannot be depended on to kill spores, they are not satisfactory agents for cold sterilization of instruments. (Arch. Surg., March '50, P. B. Price)

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The Newer Antibiotics in Therapy in the Venereal Diseases Other than Syphilis: There are now 3 effective antibiotics for treatment in granuloma inguinale; they are streptomycin, aureomycin, and chloramphenicol. Chancroid, gonorrhea, and fusospirochetosis are favorably influenced by these antibiotics, and it appears that aureomycin and chloramphenicol hold some promise in the management of lymphogranuloma venereum.

Granuloma Inguinale

Streptomycin. The minimum effective dose of streptomycin has been found to be 20 Gm. administered over a period of 5 days. When this schedule was employed in 95 of 142 patients treated, a cure rate of about 90 percent was obtained. When larger doses were employed, i.e., 4 Gm. a day for 10 days or longer, the failure rate was reduced even further. However, if doses of less than 2 Gm. a day were used over periods of time ranging from 6 to 62 days, the relapse rate was 25 percent. Five streptomycin-resistant cases were encountered. These patients had received from 40 to 158 Gm. of the drug without benefit. The advantage of streptomycin is the shortness of the period necessary for treatment. The disadvantages are parenteral administration, the need for hospitalization, and occasional severe untoward reactions.

Aureomycin. It has been established that the minimum effective dose of oral aureomycin necessary for cure is from 20 to 25 Gm. administered in 500-mg. doses every 6 hours over a period of from 10 to 12.5 days. When larger individual doses are used, nausea is common. The 20- or 25-Gm. dosage schedule has been used in most instances, but if the lesions appeared refractory or the lesions were responsive but remained incompletely healed after several weeks, the dosage was continued or another course of therapy given until healing was complete or seemed assured. In such instances, between 30 and 70 Gm. of the drug were used. Only one patient was healed with less than 20 Gm., and this patient received only 10.8 Gm. in 20.5 days. He has remained well for the past 10 months.

Only those patients whose lesions healed completely but subsequently broke down were considered as relapses. One occurred in a patient treated with 1 Gm. every 6 hours to a total of 20 Gm. This patient later admitted to having vomited part of her drug. She did not mention this at the time

for fear of prolonging the period of hospitalization. She was successfully re-treated with 20 Gm. in 10 days and has now remained well for an additional 6 months. The only other relapse that occurred among the 47 patients treated with aureomycin took place in a patient who had originally received 25 Gm. within a period of 12.5 days. The lesions in this case were healed upon completion of treatment; however, the patient returned in 4 weeks with a small relapsing lesion of 4 days' duration. Donovan bodies were demonstrated, and the patient was successfully re-treated with an additional 25 Gm. He has now remained well for 2 months.

Chloramphenicol. Chloramphenicol was administered to 34 patients with granuloma inguinale and has proved as effective against granuloma inguinale as aureomycin has. It has the added advantage of almost complete lack of side effects. In all but 3 cases the authors have arbitrarily given the drug as 500 mg. every 6 hours. The first 3 patients were treated with 1 Gm. every 6 hours to a total of 20 Gm. in 5 days. Because one relapse occurred in this group, it was decided to prolong therapy and give only a 500-mg. individual dose in subsequent patients and thereby make the schedule comparable to that employed with aureomycin.

Two relapses occurred in this series. One took place 2.5 months after the patient had completed therapy with 20 Gm. of chloramphenicol. This patient was pregnant, and the relapse occurred at the time of delivery. She was successfully re-treated with 20 Gm. in 10 days. The other relapse took place in a patient with slow response to the original course of 50 Gm. in 20 days. This relapse also occurred 2.5 months after completion of the original course of treatment, and she was successfully re-treated with an additional 20 Gm. in 10 days.

Lymphogranuloma Venereum

Patients with lymphogranuloma venereum do not respond to either penicillin or streptomycin. However, there is a slow response to treatment with both aureomycin and chloramphenicol.

Aureomycin. In the experience of the authors, aureomycin has proved of more value than chloramphenicol. To date they have treated 26 lymphogranuloma venereum patients with aureomycin. Thirteen of these had manifestations of early lymphogranuloma venereum, as evidenced by primary ulcers and/or buboes. Ulcers of late lymphogranuloma venereum, rectal strictures with or without proctitis, and multiple-draining sinuses of long duration, resistant to treatment with chloramphenicol, are included in this group.

The results in early lymphogranuloma venereum were considered good in only 4 of the 13 patients. These results are rather equivocal, inasmuch as from time to time patients are observed in whom the buboes subsided without therapy. It is the authors' experience that aureomycin offers little advantage over the

sulfonamides in the treatment of patients having early manifestations of lymphogranuloma venereum, with the exception that the former is less toxic.

Two patients with multiple-draining sinuses of the penis, scrotum, and adjacent areas, of 2 years' duration have been treated with 75 and 100 Gm. of aureomycin, respectively, as a total dose and have both shown marked improvement. Lesions in both of these patients had improved slightly and then relapsed following 40 and 100 Gm. of chloramphenicol.

Eleven patients with late manifestations of lymphogranuloma venereum presented rectal strictures and/or proctitis or ulcers. It was necessary to stop treatment in 2 patients because of severe vomiting. Fibrotic strictures of long standing do not respond to any of the antibiotics or sulfonamides. However, inflammatory strictures do respond if daily digital dilation is done during the course of aureomycin therapy. This procedure, if religiously followed, would preclude the necessity for colostomies in many of these cases. Proctitis of late lymphogranuloma venereum responds to large doses of aureomycin over a prolonged period of time. The discharge had stopped upon completion of treatment in only 3 patients who received as little as 20 Gm. or less. In 4 cases it was necessary to give from 75 to 100 Gm. in from 37 to 60 days before marked improvement was noted. Ulcers of late lymphogranuloma venereum did not seem to respond to aureomycin therapy, whereas proctitis and inflammatory strictures appeared to respond well to prolonged treatment.

Chloramphenicol. Chloramphenicol was employed in the treatment of 11 patients with lymphogranuloma venereum. Buboes and/or primary lesions of this disease were present in 4 cases. The response was not considered good in any of these cases; chloramphenicol is not equal to aureomycin in the management of patients having this type of involvement. The series, however, is too small to draw definite conclusions.

The 2 patients previously mentioned who had multiple-draining sinuses incident to long-standing infection with lymphogranuloma venereum showed slight improvement upon completion of therapy with 40 and 100 Gm. of chloramphenicol, respectively. However, within 2 weeks both relapsed, and the amount of purulent discharge in each was considerably worse than on first admission. Subsequently in both there was a good response with aureomycin.

Chloramphenicol therapy was employed in 5 patients having proctitis and rectal strictures. This group, again, is too small to draw definite conclusions; however, it appears that aureomycin is superior to chloramphenicol in the treatment of patients with any type of involvement caused by lymphogranuloma venereum. The only patient who had complete cure of her proctitis under chloramphenicol therapy was unable to tolerate aureomycin even in doses of only 250 mg. Chloramphenicol thus may be of value in the patient who cannot take aureomycin, and its use should, perhaps, be reserved for patients in this category.

Chancroid

Penicillin is of little or no value for treatment in chancroid, although improvement has been noted after its use. However, the lesions do show a response with streptomycin, aureomycin, or chloramphenicol. Streptomycin in vitro appears to be the most effective of these antibiotics. Hirsh and Taggart showed streptomycin to be effective clinically in chancroid; however, from 5 to 25 Gm. were necessary for cure. As small a total dose as 5 Gm. of aureomycin given within a 5-day period has effected cure of lesions of chancroid which had not responded to one week's treatment with sulfonamide drugs. From 5 to 10 Gm. of chloramphenicol are necessary for cure in chancroid. One recent patient with a large chancroidal lesion responded well to 10 Gm.

Gonorrhea

Both aureomycin and chloramphenicol have been used with success in gonorrhea. The oral dosages employed for either antibiotic were 1 Gm. 3 times a day for one or 2 days (i.e., 3 or 6 Gm.). In the case of aureomycin, the 3-Gm. dosage seems to be as good as that of 6 Gm.; whereas, in the case of chloramphenicol, the 6-Gm. dosage is better. Because the number of cases is limited, further work is needed before final dosage schedules can be established. The effectiveness of penicillin and streptomycin in gonorrhea has been adequately proved.

Chloramphenicol has the advantage over aureomycin of being much less toxic, whereas aureomycin is probably more effective weight for weight. Therefore, it appears that their combined use may produce even more desirable results. Both antibiotics have an advantage over penicillin in that they are highly effective orally. Under certain circumstances oral medication has its advantages.

Fusospirochetosis

All of the antibiotics mentioned are of some value in ridding the tissues of fusospirochetes. Particularly in granuloma inguinale is it necessary to administer treatment for these frequent secondary invading organisms in order to hasten healing of the specific lesion. Fusospirochetes are found in approximately 21 percent of the patients having granuloma inguinale. They disappear slowly from the lesions of patients under treatment with streptomycin, aureomycin, and chloramphenicol. Penicillin, however, is by far the most effective agent in ridding the patient of fusospirochetal organisms.

Side Effects from Antibiotics

Streptomycin. In the first 100 granuloma inguinale patients treated at the University of Georgia, 3 developed pruritus, another a generalized urticaria and circumoral vesicular eruption, and still another experienced burning sensations in the eye. These conditions were controlled by the administration of diphenhydramine hydrochloride, and all patients were able to complete therapy.

Aureomycin. The side effects from aureomycin, although uncomfortable, have not been serious. Some degree of nausea occurred in over 50 percent of the patients, and this was further complicated by vomiting and diarrhea in many. However, in only 2 of 73 cases was it necessary to discontinue the use of the drug because of persistent vomiting. Vomiting can usually be controlled and the patient may complete therapy by reducing the daily dose.

Chloramphenicol. Toxic manifestations are almost absent during the administration of chloramphenicol. Only 3 patients in the group of 45 complained of nausea. A fourth developed a pharyngitis with multiple small ulcers in the throat; these cleared when chloramphenicol was temporarily discontinued but recurred when treatment with the drug was resumed. However, with the aid of diphenhydramine hydrochloride, the patient was able to complete a course of treatment. The temperature and complete blood count remained normal throughout the episode. This is not a proved toxic reaction but is mentioned because the authors have heard of a similar occurrence in a patient treated with chloramphenicol. It deserves further evaluation. (J. Venereal Disease Information, Feb. '50, R. B. Greenblatt et al.)

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Study on the Effects of Treatment on the Bacterial Flora of the Intestinal Tract in Preoperative Preparation: The object of this investigation, carried out by W. H. Dearing and F. R. Heilman at the Mayo Clinic, was to determine the effectiveness of aureomycin in removing culturable bacteria from the intestinal tract of man and to compare the effectiveness, in this respect, of aureomycin, sulfasuxidine, sulfathalidine and dihydrostreptomycin.

A series of unselected hospitalized patients with various types of intestinal lesions which required surgical treatment were included in these studies. Some of the patients who had colitis, as well as those who had hepatitis, even though they were studied, did not undergo surgical operation. Throughout the study, the patients received a diet that leaves minimal residue and a mild saline laxative (phospho-soda) to make the stools liquid or soft. A series of saline enemas was administered from one to 2 days before operation. In addition, each patient was given one of the following: (1) aureomycin orally, 750 mg. 4 times daily (some patients received either 500 mg. 4 times daily or 250 mg. 4 times a day), (2) sulfasuxidine orally, 4 Gm. 6 times for one day and then 2 Gm. 6 times daily, (3) sulfathalidine orally, same dosage as sulfasuxidine, (4) dihydrostreptomycin orally, 500 mg. 4 times daily. A specimen of stool from each patient was sent to the bacteriologic laboratory each morning, promptly after it was passed.

Each of the following mediums was inoculated with 0.02 ml. of a fecal specimen diluted tenfold: one blood agar plate, one eosin methylene blue (Levine) plate, 3 tubes of thioglycollate broth were placed deep in a water bath at 70° C. and were left for 15 minutes in the expectation of destroying all but the spore-forming organisms.

The data contained in the tables that are presented in the article show that in general following the use of 750 mg. doses of aureomycin for from 1 and 1/2 to 6 and 1/2 days, cultures were negative for Escherichia coli, Aerobacter aerogenes, Streptococcus fecalis, and bacterial spores; many of the cultures were positive for Proteus, some were positive for Pseudomonas, and many were positive for yeasts; with doses of 500 mg. and 250 mg. the results were inferior. Using sulfasuxidine for preparation for periods of from 1 and 1/2 to 6 and 1/2 days, almost all the cultures for E. coli and Str. fecalis were positive, about half the cultures for spore-bearing organisms were positive, and about all the cultures were negative for A. aerogenes, Proteus, Pseudomonas, and yeasts. The results with sulfathalidine were about the same as those with sulfasuxidine. Dihydrostreptomycin gave results that closely paralleled those with sulfasuxidine and sulfathalidine. Aureomycin in 750 mg. doses and dihydrostreptomycin in 500 mg. doses were used in combination; from the results obtained with each separately it would be expected that almost all cultures would have been negative but 16 out of 22 for yeasts were positive.

Bacteroides are present in large numbers in normal feces but these organisms are anaerobic and may grow slowly on first isolation. Because the methods used routinely in this study were not satisfactory for detecting these organisms, a study was made to determine whether aureomycin affected them. In 5 cases in which the patients were untreated, numerous Bacteroides were found in fecal specimens which were cultured under anaerobic conditions for 5 days, whereas in the feces of 5 patients who received aureomycin Bacteroides were not found under similar cultural circumstances.

The following pre-existing conditions hindered or prevented removal of all susceptible culturable bacteria from the intestinal tract: (1) perforated intestinal lesions associated with abscess cavities, (2) intestinal fistulas of various types, (3) intestinal obstruction. These conditions probably interfered with contact between the antibiotic and the micro-organisms.

The authors consider that aureomycin given in 750 mg. doses 4 times daily for 3 or 3 and 1/2 days is the most effective single substance for preparing patients for intestinal surgery. The side reactions of aureomycin in doses of 750 mg., administered 4 times daily, consisted, in cases in which they occurred, of nausea, vomiting, and mild diarrhea.

Care should be used in giving aureomycin to patients who have duodenal ulcers. The attention of the authors has been called to 2 patients, not in their series, whose duodenal ulcers perforated after they had received aureomycin. (Proc. Staff Meet., Mayo Clin., 15 Feb. '50)

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In Vitro Sensitivity of Coliform Bacilli to Seven Antibiotics: Penicillin, streptomycin, bacitracin, polymyxin, aerosporin, aureomycin, and chloramphenicol are the antibiotics used in this study. In general, the sensitivity or resistance of any species or strain of organism to any one antibiotic is quite independent of its susceptibility to any other antimicrobial agent, except, of course, in the case of chemically closely related agents, like the various penicillins.

The in vitro sensitivity of bacteria to any given antibiotic agent has served as a useful guide to the value of that agent for therapy in infections with the corresponding bacterial species. The limitations of this generalization, however, are well recognized and are exemplified in the case of typhoid fever which is not favorably influenced by streptomycin although the causative organisms may be sensitive in vitro to concentrations which are readily attained in the blood and other body fluids. Many factors such as absorption, distribution, and excretion of the antibiotic, its plasma-binding properties, toxicity, and tendency to select out resistant variants all play a part in determining the therapeutic effectiveness of that antibiotic in infections with organisms that are apparently susceptible in vitro. Likewise, the conditions under which the in vitro tests for sensitivity are performed must also be considered because they may profoundly influence the results of the tests, and the optimum conditions for such tests may vary for the different antibiotic agents and for different species of organisms.

The present series of studies were designed primarily to make direct comparisons of the effectiveness of a group of antibiotics against a variety of common species of pathogenic aerobic bacteria insofar as that is possible from in vitro tests. In the case of each species of organism, tests were carried out simultaneously with a number of recently isolated strains and with all of the antibiotics under study. In this way it was possible to obtain valid comparisons of the susceptibility of each strain to the different antibiotics and at the same time to compare the sensitivity of different strains to each of the antibiotics used. In the case of the antibiotics which were being used clinically, an appreciably larger number of strains were tested for their sensitivity to these agents at the time the strains were isolated from infections in which the antibiotics were to be used. The results of these tests, when considered in conjunction with those of the necessarily small groups of organisms that were specifically included for the comparative studies, provide a more reliable picture of the range of sensitivity of different strains of the same organisms to these clinically important antibiotics.

It has been found most convenient to present the results of the studies separately for each of the bacterial species. The present paper includes the results obtained with the most common of the pathogenic coliform bacilli, namely, Escherichia coli, Aerobacter aerogenes, and Klebsiella pneumoniae. The results of the tests with other pathogenic bacteria will be presented in subsequent papers of this series.

The materials from which the strains of bacteria used in this study were cultured were all obtained from patients with active infectious processes. With few possible exceptions these organisms were isolated from sources which indicated that they probably were significantly concerned in the infections. The source materials are listed in the table below:

SOURCES OF THE STRAINS TESTED*

SOURCE	ESCH. COLI		A. AEROGENES		K. PNEUMONIAE	
	NUMBER	%	NUMBER	%	NUMBER	%
Blood	29	10	31	9	21	18
Urine	202	69	229	69	37	32
Exudates	17	6	11	3	10	9
Wounds, abscesses	30	10	17	5	3	3
Sputum, pharynx	8	3	39	12	44	38
Feces	5	2	3	1	--	--
Total	291	100	330	100	115†	100

*Includes only strains the sources of which were known and recorded.

†Fifty-one of the strains were successfully classified into serologic types (Julianelle) as follows: Type A, 36 strains; Type B, 4 strains; Type C, 7 strains; and Type D, 4 strains.

Escherichia coli. Several points are readily apparent from the results of the studies carried out. (1) There is a striking difference in the concentrations of the different antibiotics that are required to inhibit most of the strains. As little as from 1 to 2γ per milliliter are required for complete inhibition of most of the strains by polymyxin and aerosporin; about 6γ per milliliter are required to produce a similar effect with chloramphenicol or aureomycin, and as much as 150γ per milliliter of penicillin are necessary to achieve the same effect on most of the strains. (2) There is a wide variation in the sensitivity of different strains to penicillin, ranging from 38 to more than 6,000γ per milliliter; this range is only slightly narrower in the case of streptomycin, whereas each of the other antibiotics inhibits almost all of the strains within a narrow range of concentrations. (3) The sensitivity or resistance of any given strain to one antibiotic is independent of the effect of other antibiotics on that strain. (4) The concentrations of penicillin required to inhibit some of these strains are not many times greater than the concentrations of streptomycin needed to inhibit most of them. (5) The spread between the concentrations of streptomycin required for complete and for partial inhibition was from four- to eightfold for most strains as compared with a twofold difference in the case of the other antibiotics. Such a wide spread, however, was not observed in the tests done by the tube dilution method. In tests for streptomycin sensitivity carried out by the latter method on more than 150 strains of E. coli, 37 percent gave a sharp end point (that is, full growth in the next dilution beyond that in which complete inhibition occurred) and 58 percent of the strains showed partial inhibition in only a single dilution beyond the end point of complete inhibition.

Aerobacter aerogenes. The results of tests for sensitivity of 23 recently isolated pathogenic strains of A. aerogenes simultaneously carried out by the plate-dilution method with all 7 antibiotics are quite similar to those obtained with E. coli. There were some obvious quantitative differences, however, which were probably significant. For each of the antibiotics there were more strains

of A. aerogenes that required high concentration to produce inhibition than were noted in the case of the strains of E. coli. This is particularly evident with respect to penicillin. In the case of streptomycin, however, although there was a greater proportion of highly resistant strains of A. aerogenes, the majority were inhibited by slightly lower concentrations than those required for most of the strains of E. coli. All of the other observations that were made with respect to the strains of E. coli are equally apparent for these strains of A. aerogenes.

Klebsiella pneumoniae. The results of the tests for sensitivity of 23 recently isolated strains of K. pneumoniae carried out by the plate-dilution method simultaneously with 7 antibiotics are qualitatively quite similar to those obtained with the other coliform organisms already presented. The outstanding quantitative differences are seen in the tests with penicillin and streptomycin. These indicate that the K. pneumoniae were, on the whole, much more sensitive to both of these antibiotics than were the strains of E. coli and A. aerogenes. There is also some indication that the strains derived from sputum and blood which were predominantly Group A strains were the most sensitive to these 2 antibiotics. It is of interest to note that 2 of the strains were among the most resistant to all of the antibiotics and a third was among the least sensitive to all antibiotics except streptomycin. With the other strains, as with those of E. coli and A. aerogenes, there appeared to be no relation between the sensitivity of any strain to any one antibiotic and its sensitivity or resistance to any of the others. An analysis of the data was made with respect to the sources of all the strains of Klebsiella that were tested for streptomycin, of which there was a greater number than those tested with other antibiotics. This showed that the great majority of strains obtained from sputum and blood, most of which were Type A strains, were inhibited by streptomycin concentrations of 3.1 γ per milliliter or less, whereas those obtained from urine, most of which could not be classified serologically, required 6.3 γ per milliliter or more for complete inhibition. The order of the in vitro effectiveness on the strains of K. pneumoniae of these antibiotics, on a weight basis, is as follows: polymyxin, aerosporin, chloramphenicol, aureomycin, penicillin, and bacitracin, with streptomycin occupying an anomalous position. About half of the strains were slightly more sensitive to streptomycin than to chloramphenicol or aureomycin; about 10 percent of the strains were more resistant to streptomycin than to either chloramphenicol or aureomycin, and the remaining strains were inhibited by concentrations of streptomycin similar to those required using chloramphenicol and aureomycin to inhibit the majority of the strains.

Concerning the clinical significance of the quantitative data that have been presented, it is essential to bear in mind the manner in which these data were derived and the limitations of direct application of such in vitro data to actual therapy. Mention of some of these limitations was made in the introductory paragraphs. It is also worth noting that the conditions of the tests, as carried out in this study, tend to favor some antibiotics and to be unfavorable to others. Chloramphenicol, for example, is quite stable under these conditions; streptomycin is more active at the alkaline pH of these tests, whereas aureomycin loses activity

rapidly under the same conditions. It should be emphasized further that the actual values that are given here are strictly valid only for the exact conditions of these tests and within the rather wide limits of error of such biological methods. Quantitative comparisons with similar data in which other materials and methods are used must, therefore, be made with these reservations.

Because of the manner in which the end points have been chosen, the values for the sensitivities in the present study are much higher than those given by many other workers. On the whole, even the figures for partial inhibition, as defined in this study, may be many times greater than values for sensitivity that are based on 50 percent inhibition end points. The differences are greater still if the end point is chosen as the dilution which produces the least detectable reduction in the amount of growth as compared with controls in similar media that contains no antibiotic and they are further exaggerated if electrophotometric methods are used for comparisons of densities of growth.

This is not the place to review the factors that are known to influence antibiotic activity during actual therapy in infections. The importance of alkalinization in the success of streptomycin therapy in urinary tract infection may serve as an example of one such factor that is obviously applicable to that antibiotic but has not been shown to be of importance in the case of other antibiotics. Furthermore, time-dose relationships depend upon the absorption, excretion, and distribution of the agents in the body, which in turn determine the concentration of the antibiotic at the site where the organisms are multiplying. The nature of the lesion, the conditions that prevail at the site of infection, and the accessibility of the antibiotic to the bacteria are other determining factors. All of these factors may vary with the offending organism or with the antibiotic.

Furthermore, the toxicity of one agent or the innocuous nature of another may sometimes be the prime factor that influences the choice between effective antibiotics. Thus, both polymyxin and aerosporin, which, from the results of all the in vitro data that have been presented, are by far the choice of agents against all of the coliform organisms that were studied, have failed to achieve more than the most limited clinical trials because of the readiness with which they produce serious renal damage. Whether or not either of these agents will prove useful for topical therapy or for use in the intestinal tract must, of necessity, depend on the extent to which they are absorbed from the sites of application.

It is hoped that, in spite of all these reservations, the data that have been presented will prove useful to those who are concerned with the clinical and laboratory control of antibiotic therapy.

On the whole, the strains of K. pneumoniae were the most sensitive, those of A. aerogenes were the most resistant, and the strains of E. coli were intermediate in their susceptibility to all 7 antibiotics. (J. Lab. and Clin. Med., Feb. '50, P. F. Frank et al.)

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In Vitro Sensitivity of Proteus and Pseudomonas Aeruginosa to Penicillin, Streptomycin, Bacitracin, Polymyxin, Aerosporin, Aureomycin, and Chloramphenicol: Infections with proteus and pyocyaneous organisms have assumed a new importance since the introduction and extensive use of therapeutically potent chemical and antibiotic agents. Infections with these organisms seem to be highly resistant in treatment with the antimicrobial agents now available, and frequently they either persist or replace infections with other organisms after such therapy is used. This is particularly true in chronic urinary tract infections, in chronic bronchopulmonary suppurations, and in infected wounds and burns. Because great reliance is placed upon the use of antibiotics in the management of such suppurative processes and because it has become a frequent if not a universal practice to exhaust the possibilities of the available antibiotics in these conditions, it is well to have some understanding of the limitations of such therapy.

The first essential for successful therapy with antibacterial agents is a susceptibility of the infecting organisms to these agents. In the present paper are presented the results of in vitro tests for sensitivity to 7 antibiotics of a number of recently isolated pathogenic strains of Proteus and Pseudomonas aeruginosa. These tests were carried out in a manner similar to those reported for various coliform organisms. A group of strains of each organism was tested simultaneously with all 7 antibiotics in order to indicate some of the variations in the relative sensitivity of individual strains to the different antibiotics. Similar tests were carried out with other strains in the course of the clinical study and control of infections in which treatment with some of these antibiotics was undertaken or contemplated. All of these tests were combined and analyzed. In this manner it was possible to obtain a more reliable picture of the effectiveness of each antibiotic against different strains and to compare the potency of the different antibiotics against each of these organisms.

The great majority of the strains were obtained from cultures of urine, but a significant proportion were obtained from the sputum of patients with bronchopulmonary infections and from infected wounds and exudates. Most of these materials were obtained from the patients before antibiotic therapy was started, but some of the patients had received antibiotics for the same or other infections on previous occasions.

The table on the next page is presented by way of summary and in order to bring out in a simple manner the comparisons of the activity of the different antibiotics against the organisms concerned in this study. This table shows the range of concentrations of each antibiotic that is required to inhibit the great majority of strains of Proteus and Ps. aeruginosa. The values chosen for this purpose are those which completely inhibited at least two thirds of the strains.

ANTIBIOTIC	B. PROTEUS M.I.C. (γ/ML.)	B. PROTEUS % OF STRAINS	PS. AERUGINOSA M.I.C. (γ/ML.)	PS. AERUGINOSA % OF STRAINS
Penicillin	12.5-50	68*	>1,000	97
Streptomycin	12.5-200	83†	12.5-200	82‡
Bacitracin	10,000+	100	>10,000	100
Polymyxin	>200	100	12.5-25	84
Aerosporin	>200	89	3.1-6.3	96
Aureomycin	100-400	92	50-400	95
Chloromycetin	12.5-50	79	200-400	92

M.I.C., minimum (complete) inhibiting concentration.
*28 per cent of the strains were resistant to > 500 γ per milliliter.
†11.4 per cent of the strains were resistant to > 500 γ per milliliter.
‡14 per cent of the strains were resistant to 1,000 γ per milliliter.

On the basis of all the data presented it is possible to arrange the 7 antibiotics in the order of their effectiveness in vitro against these organisms. In the case of the strains of Proteus, the most effective agents against the majority of the strains were chloramphenicol and penicillin, but more than one fourth of all the strains were resistant to the latter. Streptomycin and aureomycin ranked next, but rather high concentrations of these agents were necessary to produce inhibition and a significant proportion of the strains was highly resistant to streptomycin. Polymyxin, aerosporin, and bacitracin were essentially inactive. Strains of Proteus were the only ones among the common pathogenic Gram-negative bacilli that were studied which were found to be resistant to polymyxin and aerosporin.

Against the strains of Ps. aeruginosa, aerosporin was by far the most effective with polymyxin ranking next. Streptomycin, aureomycin, and chloramphenicol followed in that order with respect to their activity against the majority of the strains, but about 14 percent of those tested with streptomycin were found to be highly resistant. Furthermore, the effective concentrations of aureomycin and chloramphenicol as judged from these tests were rather high and for most of the strains were either close to or beyond the range of concentrations of these agents that are attainable even in the urine during systemic therapy.

For a discussion of a few of the many limitations of the type of in vitro data that have been presented here, the reader is referred to the previous paper of this series (foregoing article). The comparisons with respect to the effectiveness of the different antibiotics against each of the organisms and with respect to each antibiotic against the different organisms are probably valid because of the uniform manner in which these tests were carried out. Within their limitations, however, these data should be of some practical value to those concerned with the choice and control of antibiotic therapy. In view of the varied metabolic activities of different species of bacteria and the probable differences in the mechanisms by which the various antibiotics exert their antimicrobial action, it is hoped that data such as these may offer to the microbiologist and the biochemist useful hints concerning the fundamental processes in bacterial nutrition on the one hand and in antimicrobial action on the other. (J. Lab. and Clin. Med., Feb. '50, P. F. Frank et al.)

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Preliminary Data on the Acute Toxicity of 90 Percent Hydrogen Peroxide: The data reported herein are preliminary and subject to revision on the basis of experimental work in progress.

No deaths resulted on exposure of rats for 8 hours to saturated vapors resulting from the volatilization of 90 percent H_2O_2 (approximately 4 mg. per liter or 2,800 ppm calculated concentration). The gas chamber temperature was in the range of from 75° to 80° F. The animals were observed for 14 days. There were no symptoms other than excitement at the beginning of exposure. Thereafter the rats remained calm and appeared normal. Tissue studies of gassed animals are in progress.

The LD_{50} of 90 percent hydrogen peroxide, intravenously, was found to be approximately 0.015 cc. per Kg. (21 mg. per Kg.). The rabbits died of gas (O_2) embolism when the agent was introduced by this route.

Application of sufficient amounts of 90 percent H_2O_2 to the clipped skin of rabbits resulted in absorption of intact peroxide into the blood stream and death of the animal by a mechanism identical with the intravenous one above. The LD_{50} for rabbits by skin application was found to be approximately 0.5 cc. per Kg. (700 mg. per Kg.). Other species were investigated similarly. There is apparently a marked species variation in toxicity of this material by percutaneous absorption because cats have not died following application of amounts as high as 3.16 cc. per Kg. Amounts up to and including 2 cc. per Kg. did not kill 3 pigs. A dog receiving 2 cc. per Kg. appeared unaffected systemically. The lower percutaneous toxicity in cats, pigs, guinea pigs, rats, and dogs was associated with a much more marked local effect on the skin than was the case in rabbits. The effect initially resulted from the liberation intracutaneously, subcutaneously, and intramuscularly of oxygen. This would seem to indicate that less of the applied material would be available for the production of gas emboli in the blood stream and would account for the lower toxicity on an embolic basis in the species of animals tested, with the noteworthy exception of the rabbit.

The local effect was very prompt and consisted of peculiar and characteristic blanching, swelling, and development of local emphysema. In the rabbits death usually occurred within 30 minutes or the animals survived indefinitely.

The loosely attached and very elastic skin of the rat was greatly distended. There was a great swelling at the area of application caused by the accumulation of the liberated gas. This gas could be aspirated and demonstrated to support combustion the day following application of the H_2O_2. This greater subcutaneous accumulation of the gas in the case of the rat may also be associated with a higher catalase content of skin and subcutaneous tissues. The distended skin apparently has its blood supply impaired so that it fails to regain its elasticity, often remaining in the expanded state until sloughed.

In general, animals surviving skin application showed complete sloughing of the skin involved. Very rarely did secondary infection intervene. Regeneration of the skin with normal fur occurred over a good part of the surface involved, but in most cases there remained areas of scar tissue where there was no regrowth of fur. In the case of rats, healing was not complete after 5 weeks.

An additional feature noticed following skin application of 90 percent H_2O_2 to rats suggested the possibility of central nervous system damage. A number of rats showed marked torticollis which persisted after 5 weeks and abnormal spinning when held up by the tails. Pathological examination showed no brain degeneration as a result of infarct. It may be that these observations can be explained on the basis of embolic blocking of the circulation to the vestibular apparatus instead of the brain.

Amounts of 90 percent H_2O_2 as small as 1 mm^3 when applied to the corneas of rabbits produced effects very closely resembling those seen in the skin. The effects of these amounts disappeared without residual injury in a few days, but larger amounts produced apparently permanent opacity of the cornea.

On the basis of the rat experiments reported herein, single acute vapor exposures in the event of gross spillage would involve no major respiratory hazard. However, it is essential to guard against liquid splashes on the skin for, based upon the results in this study, the hazard by this route is very severe. Any 90 percent hydrogen peroxide spilled on the skin should be washed freely with water as soon as possible. Liquid splashes in the eye must be avoided. Severe corneal damage with resultant visual handicap or permanent blindness can be caused by relatively small amounts of liquid. (NM 005 054, Report No. 4, 1 Feb. '50, Medical Div., Army Chemical Center, E. H. Krackow, Proj. Officer, Health Hazards of Military Chemicals Proj.)

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Progress Note on Bone Bank Activity in the Navy: A pilot bone bank has been in operation at the U. S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland, since 1 September 1949, during which time there have been approximately 100 deposits and 50 withdrawals for use. In addition to providing the Orthopedic Department of the hospital with preserved bone, the bank serves the following functions:

1. Standardizes bone bank equipment (freezer, instruments, alarm, glassware). This will permit medical supply depots to stock and issue complete bone bank equipment.

2. Provides practical training for bone bank technicians. The students are being trained with the type of equipment which is standardized for future supply activities.

Plans for the clinical use of preserved bone are being developed by the Research Division of the Bureau of Medicine and Surgery. These plans provide for a Bone Bank Center with outlets which will consist of branch banks located both within and without the continental limits of the United States. Branch banks will provide bone from local sources as conditions permit. Procurement of sufficient bone from clinical sources has always been a major problem and this is being met by the development of a satisfactory technic at the Bone Bank Center for the procurement and preservation of grafts from postmortem sources. Grafts prepared at the Bone Bank Center will be stored at freezing temperatures and shipped by air transportation to branch banks as requested.

Experimental studies in dogs are being conducted at the Naval Medical Research Institute. These include (1) an evaluation of the use in dogs of frozen bone from one animal grafted into another animal (homogenous) as compared with the use of fresh bone from one part of the body of an animal grafted into another part of the body of the same animal (autogenous), and (2) a study of bone preserved by drying frozen specimens through exposure to negative pressure (freeze-drying by sublimation). If preservation by freeze-drying is successful, it will enable preserved bone grafts to be stored at room temperatures. Preliminary observations indicate physiological acceptance of the graft by the host; however, the reconstituted freeze-dried graft is definitely more friable than fresh or frozen bone. (Lt. G. W. Hyatt, MC, USN, U. S. Naval Hospital, Bethesda, Md.)

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List of Recent Reports Issued by Naval Medical Research Activities:

Naval Medical Research Institute, NNMC, Bethesda, Maryland.

Output Characteristics of a Commercial X-ray Generator at 2000 K.V.P., 7 December 1949.

The Course of Pneumococcal Infection in Mice During Treatment with Antibacterial Substances and Adrenocortical Extract, 28 November 1949.

A Simple Apparatus for Multiple, Uniform Intravenous Injections, 13 January 1950.

Naval Medical Research Unit No. 4, U.S. Naval Training Center, Great Lakes, Ill.

The Evaluation of Ultraviolet Radiation for Control of Air Borne Infections in Naval Barracks, 10 August 1949.

Studies on Streptolysin S: Preparation, Improved Methods of Serum Inhibitor Titration, and Preliminary Results with Human Sera, 31 January 1950.

Naval Medical Field Research Laboratory, Camp Lejeune, North Carolina.

Mechanical and Bacteriologic Studies on the Quinn Water Purifier, Pilot Model No. 18, 11 January 1950.

Development of a Portable, Lightweight Field Desk, 21 February 1950.

Utensil Rack, Ward, Development of, 21 February 1950.

Development of a Portable Panel Board, 8 March 1950.

Development of a Surgical Instrument Tray and Container for Ward and Shock Unit, 8 March 1950.

Testing of a Field Dental Chair, 8 March 1950.

School of Aviation Medicine, NAS, Pensacola, Florida.

Studies of Human Adaptation to Centrifugal Force. I. Visual Perception of the Horizontal, 15 November 1949.

School of Aviation Medicine, NAS, Pensacola, Florida, and Tulane University of Louisiana.

Influence of Visual Stimulation on Habituation to Rotation, 10 January 1950.

The Perception of the Vertical. VII. Effect of Varying Intervals of Delay in a Tilted Position Upon the Perception of the Postural Vertical, 25 January 1950.

Note: Those interested in seeing copies of the complete reports should address their request to the research activity from which the report originates.

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Summer Schedule of Course in the Technic of Using Radioisotopes in Research: The Bureau of Medicine and Surgery is in receipt of an announcement from the Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee, setting forth the schedule of the next 3 sessions of the Basic Course in the Technic of Using Radioisotopes in Research to be given at that institution during the summer season of 1950.

Each session is 4 weeks in duration. Convening dates are 5 June, 3 July, and 31 July 1950. The entrance fee of $25.00 per officer will be borne by BuMed. Authorization orders only will be provided for those in attendance in accordance with Joint Letter 49-412 of Navy Department Bulletin dated 31 May 1949. No reliefs will be furnished for attending medical officers.

Requests are desired from medical officers interested in this course of study and should reach BuMed as early as possible in order that final arrangements with the institution may be completed prior to the convening date of each session. (Professional Div., BuMed)

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Naval Intern Programs: The Navy has initiated an Intern Procurement Program which provides for the appointment of 265 qualified candidates to the grade of lieutenant (junior grade) in the Medical Corps of the U. S. Naval Reserve for the purpose of pursuing intern training in civilian hospitals and medical centers during fiscal year 1951 (1950-51 training year) under the auspices of the Navy Department.

Candidates must be graduates of (or enrolled in the fourth-year class) of a medical school listed as approved by the Council on Medical Education and Hospitals of the American Medical Association and must in all other respects meet the eligibility standards for initial appointment in the Medical Corps of the U. S. Naval Reserve.

Candidates must further have contracted for a rotating internship of 12 months' duration (for the 1950-51 training year) in a civilian hospital or medical center approved for intern training by the Council on Medical Education and Hospitals of the American Medical Association. Applicants scheduled to pursue straight internships and internships of more than 12 months will be ineligible for admission to the program. The latter year of a 24-month rotating internship will be acceptable in the cases of candidates already engaged in intern training.

Prospective applicants are strongly urged to submit their applications as early as possible. The closing date of this program is 15 May. Applications

for appointment in the Medical Corps of the U. S. Naval Reserve for the purpose of participating in the Civilian Intern Program must be filed through the Office of Naval Officer Procurement nearest the place of residence of the candidate. The applications will be forwarded by procurement offices direct to the Bureau of Naval Personnel for recording and thence to the Bureau of Medicine and Surgery for determination of the candidate's physical and professional qualifications by a regularly convened intern selection board.

All candidates will be notified of their selection or nonselection for the program. Selected candidates will be issued an appointment in the grade of lieutenant (junior grade) in the Medical Corps of the U. S. Naval Reserve and orders to active duty (at the institution with which they have contracted for the year of training) on or about the date of commencement of internship. During this period of training, each appointee receives the regular pay (and allowances where applicable) of a lieutenant (junior grade).

In accordance with a directive of the Secretary of the Navy, candidates selected for Civilian Internship under Navy auspices during the fiscal year 1951 (1950-51 training year) will be required to serve on active duty for a period of 24 months beyond the date of completion of intern training. During this period of service, each such Naval Reserve officer receives the regular pay and allowances to which he is entitled by his rank, and in addition, $100 per month in accordance with Public Law 365, 80th Congress.

An additional 192 internships will be provided in U. S. naval hospitals during the fiscal year 1951. The selection of candidates for this program was conducted during October-November 1949 under the terms of the Cooperative Intern Placement Plan established by the Committees on Internships and Residencies of the Association of American Medical Colleges and the American Hospital Association. All quotas have been filled and the program for placement of interns in the U. S. naval hospitals for the 1950-51 training year has been closed. However, those candidates not selected for that program because of numerical limitations are eligible to apply for the current civilian intern program.

A similar program will be conducted during the fall of 1950 for the selection of interns for training in U. S. naval hospitals during fiscal 1952 (1951-52 training year). The time and mechanism of application for this program will be in accordance with the terms of the revised Cooperative Intern Placement Plan as established by the organizations referred to in the foregoing paragraph.

Internships in U. S. naval hospitals are rotating in character, of 12 months' duration and bear the approval of the Council on Medical Education and Hospitals of the American Medical Association.

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BUMED CIRCULAR LETTER 50-22 3 March 1950

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Clinical Boards; Functioning of

Refs: (a) Regulations for administration of Title IV of the Career Compensation Act of 1949, approved by SecNav 16 November 1949
(b) Instructions implementing reference (a), approved by SecNav 16 November 1949
(c) Manual of the Medical Department, Part III, Chapter 3, The Medical Survey

Encl: (1) Instructions pertaining to clinical boards
(2) Form for submission of clinical board reports

1. The material contained in enclosure (1) is promulgated in amplification of references (a) and (b) for purposes of guidance and uniformity.

2. It is anticipated that insofar as applicable the content of references (a) and (b) and of enclosure (1) will be incorporated in the Manual of the Medical Department.

3. The provisions of references (a) and (b) supersede reference (c) where they are in conflict.

4. The attached form (enclosure (2)) is considered an appropriate format for presenting clinical board reports. The reproduction of such a form should be co-ordinated with the appropriate district publications and printing office.

C. A. Swanson

Note: A copy of this letter together with enclosures appears in the 15 March 1950 Navy Department Bulletin.

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BUMED CIRCULAR LETTER 50-23 7 March 1950

From: Chief, Bureau of Medicine and Surgery
To: All Holders of the Manual of the Medical Department

Subj: Manual of the Medical Department, 1949 Revision; Replacement of Defective Binders for

This letter (1) states that the manufacturer of the binders for the 1949 revision of the Manual of the Medical Department has guaranteed to place in

first-class working order, at no cost, any binders that show evidence of defect up to 12 December 1950, and (2) directs that addressees advise BuMed (Code 2124) in duplicate of any defective binders, whereupon BuMed will forward replacement binders, to be exchanged upon receipt for the defective ones that are then to be returned to BuMed, attention, Code 2124.

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BUMED CIRCULAR LETTER 50-24 8 March 1950

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Medical Training Films and Other Medical Audio-Visual Aids, Production and Procurement of

Ref: (a) BuMed Circular Letter No. 47-168; AS&SL July-Dec 1947, 47-1146, p. 254

1. Reference (a) is hereby cancelled and superseded by this letter.

2. The Bureau of Medicine and Surgery is responsible for providing technical assistance and exercising technical control over matters relative to the production of medical audio-visual training aids for the naval service. Through the Bureau of Naval Personnel, the Bureau designates the distribution of all medical training films produced under the cognizance of the Navy Department.

3. In the past some activities have independently produced medical training films and other training aids, or procured them from various sources other than naval. It can be assumed this action was justified at the time, but the resulting duplication of effort and excessive cost precludes further use of these methods.

4. To prevent such duplication of effort and to insure the production of effective medical training aids at a minimum cost, the Interdepartmental Committee for Medical Training Aids was established by the appointment of representatives from the Departments of the Army, Navy, and Air Force, the Veterans Administration, and the U. S. Public Health Service. This Committee is vested with the authority to rule on the production of all medical training aids initiated by the five represented services based on general acceptability and usefulness relative to all medical and related training programs. However, it does not supersede or replace the Navy Film Production Board of Review and all medical training films to be produced by the Navy must be submitted to this Board for final approval for production.

5. It is directed that procurement and production methods indicated in paragraphs three (3) above be discontinued and that all proposals or requests for production or procurement of medical audio-visual training aids be referred to this Bureau for approval and processing through established channels.

6. Prior approval to accomplish record photography is not required and this directive is not to be construed to include such photography, although it may be utilized in conjunction with medical training programs. In the production of such films credit titles are not permitted nor may any personnel concerned in the production or appearing in the film itself be identified. However, the activity sponsoring such films may be listed by title. On completion the master print must be forwarded to the Medical Illustration Service, Armed Forces Institute of Pathology, Washington 25, D. C., where the film will be classified, cataloged and duplicates struck. The master print will be stored in the vaults of the Armed Forces Institute of Pathology. Copies of such film can be obtained by directing requests to the Medical Illustration Service, Armed Forces Institute of Pathology. C. A. Swanson

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BUMED CIRCULAR LETTER 50-25 10 March 1950

From: Chief, Bureau of Medicine and Surgery
To: Commandants all Naval Districts (except Seventeenth) and River Commands
Commanding Officer, Naval Medical Center, Guam, Marianas
Commanding Officer, U. S. Naval Station, Samoa

Subj: Photofluorographic Equipment; Inspection of

Ref: (a) Paragraph 21103, Manual of the Medical Department
(b) BuMed Circular Letter 47-170

Encl: (1) Locations of photofluorographic units
(2) Inspection forms

This letter states that photofluorographic equipment to be used by the Armed Forces has been standardized and in the future only equipment using 70 MM roll film will be procured. As funds become available, photofluorographic machines now in service, the continued use of which is justified by need, will be converted to use 70 MM roll film or replaced by new 70 MM equipment, depending upon the condition of the individual unit. Instructions are given for determining the need for photofluorographic equipment to accomplish the directives of references (a) and (b) and for deciding upon conversion or replacement of photofluorographic units. BuMed requests that the photofluorographic

units now installed at activities under the jurisdiction of the addressees be inspected by a medical electrical repairman or other person competent to conduct such an inspection and a report submitted together with a recommendation for conversion to 70 MM, replacement with new 70 MM equipment or inactivation, in the case of each 35 MM unit.

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BUMED CIRCULAR LETTER 50-26 13 March 1950

From: Chief, Bureau of Medicine and Surgery
To: BuMed Management Control Activities

Subj: Industrial Relations Conferences, OIR Sponsored; Agenda for

This letter requests addressees to submit to BuMed by 28 March 1950, items which they would suggest as suitable topics for discussion at 2 industrial relations conferences now being planned to be held this year, under the sponsorship of the Office of Industrial Relations. One conference is to be held in San Francisco, early in May, for activities west of the Mississippi; this will be followed shortly thereafter by a conference in Washington, D. C., for attendance by east coast activities.

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BUREAU OF MEDICINE AND SURGERY
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